REMARKS

I. Status of the Claims

Claims 1-45 were filed with the original application. Claims 46-135 were added during prosecution. Claims 27-31, 62-76, 80-82, 92-95, 102-110, 113, 114, 121-126 and 131-135 have been canceled. Thus, claims 1-26, 32-61, 77-79, 83-91, 96-101, 111, 112, 115-120 and 127-130 are pending and stand rejected under 35 U.S.C. §103 and for obviousness-type double-patenting. The specific grounds for rejection, and applicants' response thereto, are discussed in detail below.

Minor amendments to the claims are provided. The amendments clarify the claims further in light of previous amendments relating to inhibition of growth. No new matter is introduced by these amendments, and no new issues are raised thereby.

II. Rejection for Obviousness-Type Double Patenting

The pending claims are rejected under the judicially-created doctrine of obviousness-type double-patenting as being unpatentable over claims 1-105 of U.S. Patent 5,747,469. Applicants enclose a terminal disclaimer over the '469 patent, as well as a second terminal disclaimer over copending application U.S. Serial No. 08/953,290. Reconsideration and withdrawal of the amendment is respectfully requested.

III. Rejections Under 35 U.S.C. §103

The examiner has the rejected all claims over Lowe *et al.* and Clarke *et al.* in view of Tischler *et al.*, Wills *et al.* and Gregory *et al.* According to the examiner, Lowe and Clarke

demonstrate that DNA damage caused by radiation induces apoptosis in a p53-dependent fashion. Further, Tischler is said to set forth a long list of DNA damaging agents, and Wills and Gregory are said to support the use of p53 in gene therapy generally. Applicants respectfully traverse.

A. The Cited Reference Do Not Create a Prima Facie Case

The examiner argues that Lowe, Clarke, Tischler, Wills and Gregory, in combination, suggest the presently claimed invention. However, it is important to remember each of the requirements for establishing a *prima facie* case of obviousness. Applicants point to *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), which held that, in order for references to obviate an invention, it must be shown that the references contain:

(1) detailed enabling methodology for practicing the claimed invention;
(2) a suggestion for modifying the prior art to practice the claimed invention; and
(3) evidence suggesting that the invention would be successful.

It is submitted that the present references relied upon by the examiner clearly fail to satisfy the tripartite *O'Farrell* test.

First, there is no suggestion in any of the references to use p53 gene therapy, either alone or in combination with a DNA damaging agent, to induce apoptosis in T-cells. While Wills and Gregory may address p53 gene delivery using viral vectors, this teaching is far removed from a suggestion to modify Lowe or Clarke, which do not address gene transfer in any form, to arrive at the present invention. Applicants submit that it is incumbent upon the examiner to find the

suggestion to modify the primary reference ***in the prior art***. *In re Soli*, 187 USPQ 797 (CCPA 1963).[1]

The examiner has only argued that the authors were "investigating the effects of p53 on cell death." This sort of generalized statement, if true, falls far short of a specific suggestion to modify the primary references – Lowe and Clarke – to introduce a p53 gene into a T-cell. There is no rationale provided as to why one would seek to introduce a p53 gene into a cell when the cell already expresses wild-type p53. More importantly, the references themselves are silent as to why one would seek to change the scientific design described in Lowe and Clarke, especially when their results were "positive" for apoptosis.

This omission from the art is fatal to the examiner's position, and the attempts to "fill in the blank" with general and unsupported statements constitutes an improper hindsight reconstruction of the invention, which is forbidden. *In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. Sup. Ct. 1965).

Second, the examiner has completely glossed over the issue of whether the claimed invention could be practiced successfully. As has been noted in the previous response, there was no *a priori* predictability, *circa* 1994, with respect to combining ectopic p53 expression with

[1] "When, as in the instant case, the Patent Office finds, in the words of 35 USC §103, 'differences between the subject matter sought to be patented and the prior art,' it may not, without some basis in logic or scientific principle, merely alleged that such differences are either obvious or of no patentable significance and thereby force an [applicant] to prove conclusively that it is wrong." *In re Soli*, 187 USPQ at 801.

DNA damaging agents. One of skill would have had no way of knowing whether or not p53 expression from an exogenously provided vector would give the same results as the endogenous p53 of Lowe and Clarke.

For example, regulation of the expression of a chromosomal gene, *i.e.*, endogenous p53, is likely to be far different that than observed with an exogenous gene. This is true for a variety of reasons, including but not limited to, (i) different promoter (*i.e.*, non-native promoter), (ii) different chromatin structure surrounding the promoter, transcription start site, or transcription termination site, and (iii) different distal, *cis*-acting regulatory signals not found in exogenous expression constructs. This is especially true when one considers that this very same chromatin may well be damaged by the presence, at least in some embodiments, of DNA damaging agents. There simply is no way that this situation can present the ***reasonsable likelihood of success*** demanded for a *prima facie* case.

Thus, for at least two reasons, the examiner has not carried the burden of establishing a *prima facie* case of obviousness. Therefore, based purely on the deficiencies in the examiner's analysis, the rejection should be reversed.

B. The Art Evidences Conflicting Reports Regarding the Effects of Combining p53 and DNA Damaging Agents

In their previous response, applicants provided an explanation of why, even taking the examiner's position at face value, the rejection must fall. This explanation was based on the fact that, at the time of the present invention, the field was in a state of confusion regarding how p53 and DNA damage interacted in the development of apoptosis. This line of argument, presented

in detail in the previous response, was derived from the successful prosecution of the parent of the present application, now U.S. Patent 5,747,469. Applicants will present this argument below for the Board's review and consideration.

It is submitted that the rationale advanced in the final office action clearly cannot support the rejection advanced simply because ***there is no evidence of likelihood of success for the claimed invention***. As the leading cases of *In re O'Farrell* and *In re Vaeck* indicate, likelihood success is a key element in an obviousness rejection, and without it the rejection must fail.

Turning to the instant situation, applicants respectfully submit that it would have been impossible to know, *a priori*, what would happen when one combined the influence of a DNA damaging agent with p53-based gene therapy in a tumor cell. Not only could the combination have provided no added benefit, it might even have been detrimental. This simply could not have been predicted. ***This is the touchstone of nonobviousness.***

To further underscore the absence of predictability with respect to the instant claims, applicants point out that, at the time of filing, the literature was in a state of flux as to the potential relationship between p53 and DNA damage. For example, Kastan *et al.* (1991) describes experiments designed to help elucidate the role of p53 in response to DNA damage. As the discussion indicates, DNA damage appears to induce p53, which itself appeared to be associated with an arrest in DNA synthesis. This arrest in DNA synthesis, in turn, was hypothesized to permit the cell to an opportunity to repair any damage to the DNA, preventing transmission of errors in the genetic code to progeny cells.

Taken at face value, this paper clearly raises the question of whether a DNA damaging agent and p53 would work ***against*** each other, given that the point of inducing DNA damage as part of a cancer therapy regimen is to trigger cell death. By providing an exogenous p53 to treated cells, one would have to consider the possibility that this would, in fat, ***counteract*** the DNA damage that had been induced, thereby canceling out the therapeutic effect. Tischler, the only reference cited by the examiner that even addresses this issue, simply confirms Kastan *et al.* in showing that DNA damage increases p53 levels. ***It does not, however, address the inherent conflict between the cell's desire to repair DNA damage and the clinician's desire to have that damage result in cell death***. This conflict only would be exacerbated by the further provision of an exogenous p53 to a tumor cell. Thus, on its face, the teaching of Tischler ***raises*** more questions than it answers.

To further obscure the situation surrounding the interaction between p53 and DNA damage, one must turn to the 1993 paper by Stichenmeyer *et al.* This paper reports on the effect of a p53-associated G_1 checkpoint, lost in cells [that] have defective p53 function, on sensitivity to DNA damage. As stated by the authors, their "results indicate that although the cell cycle checkpoint in G_1 can be impaired through mutation of *p53* or by other mechanisms, [the] loss [of] the G_1 checkpoint *per se* does not influence radiosensitivity or sensitivity to camptothecin." Thus, this paper would lead one to the conclusion that the presence of p53 is not a critical factor in the response of a cell to DNA damage, much less that p53 could ***cooperate*** with a DNA damaging agent to produce an enhanced therapeutic effect.

Thus, in conclusion, a fair reading of the prior art (including Tischler) could not, as of applicants' filing date, have provided any reasonable inference, much less a specific suggestion, that a combination of p53 gene therapy and a DNA damaging agent would be a worthwhile endeavor in the treatment of cancer. Without such an expectation, a *prima facie* case of obviousness cannot exist.

According to the examiner, as the Stichenmeyer and Kastan references were not relied upon, they can "in no way negative the teachings of the later published teachings of Lowe *et al.* and Clarke *et al.*" It is respectfully submitted, however, that the Examiner is mistaken. Stichenmeyer, like Lowe and Clarke, was published in 1993, with Kastan published only two years earlier. These reference clearly make up a body of contemporaneous work that cannot be parsed from each other.

In this same vein, it is improper to read the prior art selectively – rather, the prior art must be read as a whole, for all it teaches, as that is what the hypothetical artisan of ordinary skill must do. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

In that these references affirmatively teach ***away*** from the present invention, the case law demands that they must be taken into account and given due weight – not simply discarded when they fail to fit the rejection:

> When prior art contains apparently conflicting references, the Board ***must*** weigh each reference for its power to suggest solutions to an artisan of ordinary skill. The Board ***must*** consider all disclosures of the prior art ... to the extent that the references are ... in analogous fields of endeavor and thus would have been considered by a person of ordinary skill in the field of the invention. The Board, in weighing the suggestive power of each reference, ***must*** consider the degree to which one reference might accurately discredit another.

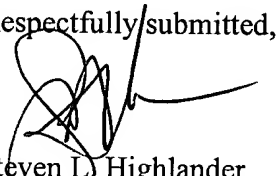
In re Etter, 225 USPQ 1, 6 (Fed. Cir. 1985) (emphasis added). This reasoning gives rise to the doctrines of "failure of others" (*Intel Corp. v. U.S. Int'l Trade Comm'n*, 20 USPQ2d 1161 (Fed. Cir 1991)) and "teaching away" (*In re Beattie*, 24 USPQ2d 1040 (Fed. Cir. 1997)). If the examiner were free to ignore contradictory teachings, the "failure of others" and "teaching away" doctrines would have no meaning.

In sum, for the reasons specified, applicants respectfully submit that the rejection fails to pay sufficient deference to the teachings of the art as a whole. Consequently, it also improperly picks and chooses from the literature, and does not address the specific deficiencies of particular references. Reversal of the rejection is, again, requested.

IV. Summary

In light of the preceding, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. Should Examiner Sandals have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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PENDING CLAIMS

1. (Amended) A method of reducing the growth rate of a [cell] tumor, comprising contacting [said] a cell within said tumor with (a) a gene encoding a functional p53 protein and (b) a DNA damaging agent in a combined amount effective to [kill] inhibit the growth of said [cell] tumor.

2. The method of claim 1, wherein said cell is contacted with said gene in combination with X-ray radiation, UV-irradiation, γ-irradiation, microwaves, adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mytomycin C, or cisplatin.

3. The method of claim 2, wherein said cell is contacted with said gene in combination with cisplatin.

4. The method of claim 1, wherein said cell is contacted with a recombinant vector that expresses a functional p53 protein in said cell in combination with a DNA damaging agent.

5. The method of claim 4, wherein said p53-expressing recombinant, non-viral vector is a naked DNA plasmid or a plasmid within a liposome, a retroviral vector, an AAV vector, or a recombinant adenoviral vector.

6. The method of claim 5, wherein said p53-expressing recombinant vector is a recombinant adenoviral vector.

7. The method of claim 4, wherein said p53-expressing recombinant vector comprises a p53 expression region positioned under the control of a constitutive promoter.

8. The method of claim 4, wherein said recombinant vector comprises a p53 expression region, the cytomegalovirus IE promoter and the SV40 early polyadenylation signal.

9. The method of claim 6, wherein at least one gene essential for adenovirus replication is deleted from said adenovirus vector construct and the p53 expression region is introduced in its place.

10. The method of claim 9, wherein the E1A and E1B regions of the adenovirus vector are deleted and the p53 expression region is introduced in their place.

11. The method of claim 6, wherein said recombinant adenoviral vector is present within a recombinant adenovirus.

12. The method of claim 1, wherein said cell is first contacted with said gene and is subsequently contacted with said DNA damaging agent.

13. The method of claim 1, wherein said cell is first contacted with said DNA damaging agent and is subsequently contacted with said gene.

14. The method of claim 1, wherein said cell is simultaneously contacted with said gene and said DNA damaging agent.

15. The method of claim 1, wherein said cell is contacted with a first composition comprising said gene and a second composition comprising said DNA damaging agent.

16. The method of claim 15, wherein said first or second composition is dispersed in a pharmacologically acceptable formulation.

17. The method of claim 1, wherein said cell is contacted with a single composition comprising said gene in combination with said DNA damaging agent.

18. The method of claim 17, wherein said composition is dispersed in a pharmacologically acceptable formulation.

19. The method of claim 17, wherein said cell is contacted with a single composition comprising a recombinant vector that expresses p53 in said cell in combination with said DNA damaging agent.

20. The method of claim 19, wherein said cell is contacted with a single composition comprising a recombinant adenovirus containing a recombinant vector that expresses p53 in said cell in combination with said DNA damaging agent.

21. (Canceled) The method of claim 1, wherein said cell is a tumor cell.

22. (Amended) The method of claim [21] 1, wherein said tumor cell is a malignant cell.

23. The method of claim 22, wherein said malignant cell is a lung cancer cell.

24. The method of claim 22, wherein said malignant cell is a breast cancer cell.

25. The method of claim 22, wherein said malignant cell has a mutation in a p53 gene.

26. (Amended) The method of claim [21] 1, wherein said tumor cell is located within an animal at a tumor site.

32. A composition comprising a gene encoding a functional p53 polypeptide in combination with a DNA damaging agent.

33. The composition of claim 32, comprising said gene in combination with adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mytomycin C, or cisplatin.

34. The composition of claim 33, comprising said gene in combination with cisplatin.

35. The composition of claim 32, comprising a recombinant vector that expresses a functional p53 protein in an animal cell in combination with a DNA damaging agent.

36. The composition of claim 35, wherein said recombinant vector is a naked DNA plasmid or a plasmid within a liposome.

37. The composition of claim 36, wherein said recombinant vector is a recombinant adenoviral vector.

38. The composition of claim 37, wherein said recombinant vector is a recombinant adenoviral vector is present within a recombinant adenovirus particle.

39. The composition of claim 32, comprising a recombinant adenoviral vector present within a recombinant adenovirus particle in combination with cisplatin.

40. The composition of claim 32, dispersed in a pharmacologically acceptable formulation.

41. The composition of claim 40, formulated for intralesional administration.

42. A therapeutic kit comprising, in suitable container means, a pharmaceutical formulation of a recombinant vector that expresses a functional p53 protein in an animal cell and a pharmaceutical formulation of a DNA damaging agent.

43. The kit of claim 42, wherein said recombinant vector and said DNA damaging agent are present within a single container means.

44. The kit of claim 42, wherein said recombinant vector and said DNA damaging agent are present within distinct container means.

45. The kit of claim 42, comprising a pharmaceutical formulation of a recombinant adenovirus including a recombinant vector that expresses a p53 protein in an animal cell and a pharmaceutical formulation of cisplatin.

46. (Amended) The method of claim [21] 1, wherein the tumor cell is contacted with a DNA damaging agent by irradiating the tumor cell with X-ray radiation, UV-irradiation, γ-irradiation or microwaves.

47. The method of claim 46, wherein the tumor cell is contacted with a DNA damaging agent by irradiating the tumor cell with X-ray radiation.

48. The method of claim 46, wherein the tumor cell is contacted with a DNA damaging agent by irradiating the tumor cell with UV-irradiation.

49. The method of claim 46, wherein the tumor cell is contacted with a DNA damaging agent by irradiating the tumor cell with γ-irradiation.

50. The method of claim 46, wherein the tumor cell is contacted with a DNA damaging agent by irradiating the tumor cell with microwaves.

51. (Amended) The method claim [21] 1, wherein the tumor cell is contacted with a pharmaceutical composition comprising a DNA damaging compound.

52. The method of claim 51, wherein the DNA damaging agent is cisplatin.

53. The method of claim 51, wherein the DNA damaging agent is doxorubicin.

54. The method of claim 51, wherein the DNA damaging agent is etoposide.

55. The method of claim 51, wherein the DNA damaging agent is verapamil.

56. The method of claim 51, wherein the DNA damaging agent is podophyllotoxin.

57. The method of claim 51, wherein the DNA damaging agent is 5-FU.

58. The method of claim 51, wherein the DNA damaging agent is actinomycin-D.

59. The method of claim 51, wherein the DNA damaging agent is adriamycin.

60. The method of claim 51, wherein the DNA damaging agent is camptothecin.

61. The method of claim 51, wherein the DNA damaging agent is mytomycin C.

77. The method of claim 4, wherein said gene is administered prior to said DNA damaging agent.

78. The method of claim 4, wherein said gene is administered after said DNA damaging agent.

79. The method of claim 4, wherein said gene is administered at the same time as said DNA damaging agent.

83. (Amended) The method of claim 26, wherein said gene is delivered to said tumor endoscopically, intravenously, intratracheally, intralesionally, percutaneously or subcutaneously.

84. The method of claim 26, wherein said tumor site is a resected tumor bed.

85. The method of claim 26, wherein said administration is repeated.

86. The method of claim 13, wherein the period between administration of the DNA damaging agent and gene is between 12 and 24 hours.

87. The method of claim 13, wherein the period between administration of the DNA damaging agent and gene is between 6 and 12 hours.

88. The method of claim 13, wherein the period between administration of the DNA damaging agent and gene is about 12 hours.

89. The method of claim 12, wherein the period between administration of the gene and DNA damaging agent is between 12 and 24 hours.

90. (Amended) The method of claim 12, wherein the period between administration of the [vector] gene and DNA damaging agent is between 6 and 12 hours.

91. (Amended) The method of claim 12, wherein the period between administration of the [vector] gene and DNA damaging agent is about 12 hours.

96. (Amended) The method of claim [21] 1, wherein said tumor cell is an epithelial tumor cell.

97. The method of claim 23, wherein said lung cancer cell is non-small cell lung carcinoma cell.

98. The method of claim 97, wherein said non-small cell lung carcinoma cell is a sqamous carcinoma cell.

99. The method of claim 97, wherein said non-small cell lung carcinoma cell is an adenocarcinoma cell.

100. The method of claim 97, wherein said non-small cell lung carcinoma cell is a large-cell undifferentiated carcinoma cell.

101. The method of claim 95, wherein said lung cancer cell is a small cell lung carcinoma cell.

111. The method of claim 26, wherein said gene is administered in about 0.1 ml.

112. The method of claim 26, wherein said gene is administered in about 10 ml.

115. The method of claim 52, wherein said cisplatin is administered at 20 mg/m^2.

116. The method of claim 53, wherein said doxorubicin is administered at 25-75 mg/m^2.

117. The method of claim 54, wherein said etoposide is administered at 35-50 mg/m^2.

118. The method of claim 57, wherein said 5-FU is administered at 3-15 mg/kg.

119. The method of claim 47, wherein the x-ray dosage is between 2000 and 6000 roentgens.

120. The method of claim 47, wherein the x-ray dosage is between 50 and 200 roentgens.

127. The method of claim 4, wherein said promoter is a promoter.

128. The method of claim 7, wherein the promoter is selected from the group consisting of SV40, CMV and RSV.

129. The method of claim 128, wherein the promoter is the CMV IE promoter.

130. The method of claim 129, wherein the vector further comprises a polyadenylation signal.